Laryngopharyngeal Reflux (LPR)

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Introduction

Laryngopharyngeal reflux (LPR) can be defined as influx of stomach contents into the upper airway, especially the laryngopharynx and posterior nasopharynx. As a result, affected individuals complain of various laryngopharyngeal and respiratory symptoms caused by the damage to the upper airway epithelium.

LPR is primarily a clinical diagnosis, usually based on the presence of several symptoms, which most often include hoarseness, nonproductive throat clearing, sensation of having excess mucous in the throat, globus pharyngeus, difficulties swallowing, dry cough, and difficulties breathing. Multiple analyses and surveys show that heartburn complaints occur in no more than 40% of affected (LPR) patients.

Due to the variability of its clinical presentation, confusing sets of symptoms, and lack of reliable testing methods, there are no agreed upon diagnostic criteria for LPR. As a result, it is often underdiagnosed and undertreated in spite of being a very common condition. Reflecting this confusion is the use of many different synonyms such as extra-esophageal reflux (EER), reflux laryngitis, laryngeal reflux, gastro-pharyngeal reflux, pharyngoesophageal reflux, supraesophageal reflux, and silent or atypical reflux.

The aim of this chapter is to give a succinct overview of the current understanding of LPR.

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History

Reports of association between vocal cord granulomas and laryngopharyngeal reflux have been mentioned as early as in the late 1960s. In a breakthrough 1991 article, Dr. Koufman presented a detailed description of various aspects of reflux in the laryngopharyngeal region and provided important observations about the clinical presentation, diagnosis, and proposed management at that time [1]. In 2002, Koufman et al. published the official position statement of the American Academy of Otolaryngology and stressed that LPR is a distinct clinical entity separate from gastroesophageal reflux disease (GERD) [2]. Guidelines presented by the American Gastroenterological Association Institute in 2008 presented a different perspective describing GERD as having two different types of syndromes, esophageal, and extra-esophageal (pertaining to LPR).

In spite of growing number of publications, there is still little awareness and understanding of LPR in the medical community except for otolaryngologists, voice specialist, and foregut and esophageal specialists.

Epidemiology

Because of lack of diagnostic criteria, it is difficult to estimate the true incidence of LPR**.** There are no large population-based studies that have examined this carefully. Most recent estimates of GERD prevalence in North America are in the range of 18.1–27.8%. LPR can be considered as a subset of GERD, and clinical experience of many experts in the field points to this condition being very prevalent. Kaufmann reported an incidence of LPR to be 50% in patients with laryngeal and voice symptoms [3]. An analysis conducted at a large group specialty practice in the New York City area (ENT and Allergy Associates) in 2016 showed that 9.7% of all adult patients seen that year (29,473 out of 304,362) carried the diagnosis of GERD or LPR. It is estimated that the economic impact of diagnosing and treating LPR can be 5–6 times higher than that of GERD [4].

Pathophysiology

The pathophysiology of LPR is a complex interplay between abnormal function of esophageal sphincters, esophageal motility, and the efficacy of various defense mechanisms (presence of saliva, mucous barrier, and activity of carbonic anhydrase), which ultimately affect the extent and frequency of exposure to acid, bile, and pepsin on the laryngopharyngeal mucosa.

Lower esophageal sphincter dysfunction and esophageal dysmotility directly contribute to prolonged esophageal acid clearance in patients with LPR [5].

Abnormal upper esophageal sphincter (UES) function is another critical factor in LPR pathophysiology. Inappropriate premature relaxation of the UES during a reflux event leads to airway damage. It has been shown that prolonged mucosal damage is associated with laryngopharyngeal sensory deficits. Patients with GERD

and cough have impaired laryngopharyngeal sensitivity, which in turn further diminishes UES function and leads to more reflux events.

Rarely, LPR may also be caused by presence of the so-called inlet patch, which is heterotopic acid-secreting gastric mucosa in the upper esophagus.

Acid

The larynx and hypopharynx have a neutral pH of 7.0 and are extremely sensitive to changes of pH caused by stomach acid and bile. In addition, the upper airway lining has no good mechanisms to protect itself from the effects of the contents of gastric reflux.

Any exposure of the laryngopharynx to stomach acid will initiate epithelial damage. This damage can be a result of direct acidification of the cellular microenvironment or augmentation of pepsin's enzymatic action. Highly acidic foods may themselves also contribute to this process. Even a mildly acidic pH of 6.5 can initiate the activity of pepsin and lead to epithelial damage.

Pepsin

As mentioned above, acid does not act alone in damaging the upper aerodigestive tract mucosa. Pepsin, a proteolytic enzyme secreted in the stomach, is considered to be one of the primary causes of mucosal damage in LPR. Pepsin has been found in higher concentrations in the laryngeal mucosa and respiratory secretions in LPR patients when compared with controls. Initially, pepsin has been thought to cause epithelial damage by its proteolytic activity in digesting the molecules that maintain cohesion between the cells. However, recent studies have shown that pepsin is also endocytosed by the airway and possibly esophageal epithelial cells. It is then retained in the intracellular vesicles of low pH, in which the enzyme's proteolytic activity is restored. It has been demonstrated that in such setting, pepsin causes mitochondrial damage, significant cell toxicity, and changes in the expression of several genes implicated in stress and toxicity [6].

It has been also suggested that exposure of the larynx and pharynx to pepsin causes damage to the mucosa through depletion of carbonic anhydrase III enzyme, which plays a key role in the regulation of pH and protection of tissues from the effects of acid [7]. A positive association between macroscopic findings of inflammation and damage in LPR and presence of pepsin in tracheal aspirates has been shown. There is growing evidence that the damaging effect of pepsin and lack of carbonic anhydrase activity may lead to carcinogenesis.

Bile Acids

Bile acids are also part of duodenal-gastric refluxate. Laryngopharyngeal mucosa is not adapted for bile exposure. Higher concentrations of bile acids in saliva have been found in LPR patients. Considering the neutral pH of laryngopharyngeal

mucosa, the unconjugated bile acids like chenodeoxycholic acid may have a significant damaging effect [8].

Clinical Presentation

LPR is notoriously difficult to diagnose because most of the symptoms associated with it are not very specific, and its presentation is pleomorphic. Patients present with various combinations and severity of symptoms. Heartburn and other "typical" complaints of GERD are often absent. As mentioned before, a diagnostic gold standard for LPR has not been established.

The most common presenting symptoms of LPR are laryngeal in nature and include hoarseness, globus pharyngeus, perception of excess mucous in the throat accompanied by constant nonproductive throat clearing, dry or itchy throat, and chronic or recurrent dry cough. Many patients have stridor, which is mistaken for wheezing and therefore misdiagnosed as asthma. Reflux-induced chronic laryngitis has been associated with development of subglottic stenosis, laryngeal granulomas, contact ulcers, vocal nodules, and laryngeal carcinoma.

LPR is one of the most common causes of chronic cough. Cough in LPR is mostly nonproductive. Affected persons often experience fits of unstoppable cough to the point of tearing, loss of bladder control, and gagging. Cough often interferes with sleep. Complaints of shortness of breath are also very common and can be very distressing. Patients report inability to take a breath in (inspiratory dyspnea) and suffocating sensations that cause panic reactions, which prompt them to seek immediate help in the emergency rooms.

Other less frequently observed (or possibly less reported) symptoms associated with LPR include complaints of bad taste in the throat and mouth, water brash (regurgitation of excessive amounts of saliva), night sweats, sore throat on waking up, itchy ears, nasal congestion, and even tooth erosion. There are also reports of significant coexistence between LPR and obstructive sleep apnea. In addition, laryngopharyngeal reflux has been associated with chronic rhinosinusitis and chronic otitis media. Pepsin has been consistently detected in significant proportion of chronic middle ear effusions in children and has been associated with chronic otitis media.

Multiple authors have reported that LPR is responsible for causing bronchoconstriction and asthma symptoms, but careful review of medical literature does not provide a clear proof. Shortness of breath and complaints of wheezy respiratory noises should be attributed primarily to laryngospasms and resulting stridor, especially when pulmonary function tests are normal.

Because of the predominance of respiratory complaints and paucity of classical GERD symptoms, many patients present themselves first to their primary care physician, pulmonologist, allergy specialist, or otolaryngologist rather than to a gastroenterologist or a surgeon.

Diagnosis

The diagnosis of LPR is based on the combination of clinical suspicion, presenting symptoms, and exclusion of other conditions that may present with similar complaints. To clarify or facilitate the diagnosis, one can also use clinical diagnostic tools (questionnaires), perform endoscopic evaluations, pH probe tests, and check for presence of pepsin in the upper airway.

Role of Reflux Symptom Index (RSI)

One of the few validated clinical diagnostic tools used most frequently to facilitate the diagnosis of LPR is reflux symptom index (RSI), which consists of a set of nine questions addressing the most common symptoms and their severity. RSI is a useful tool but has significant limitations. It was developed as a severity assessment and outcomes instrument for patients already suspected and managed for LPR. RSI's validity and reliability was based on evaluation of only 25 patients already diagnosed with LPR and 25 controls [9]. In addition, some of the RSI questions do not appear to be well formulated (multiple symptoms lumped together) and miss some important symptoms or complaints helpful in the diagnosis of LPR (e.g., throat dryness or bad taste in the throat or mouth).

Laryngoscopy

Laryngoscopy (indirect laryngoscopy or fiber-optic nasolaryngoscopy) is an integral part of a patient's evaluation to rule out any other laryngeal disorders (including vocal cord nodules and carcinoma), which may cause hoarseness, dysphonia, and cough. It is important to stress that the laryngoscopic findings typical for LPR such as posterior laryngeal edema, true vocal fold edema, and pseudosulcus are not diagnostic by themselves. Studies show poor correlation between clinical symptoms and endoscopic findings of LPR.

The typical laryngoscopic changes associated with LPR include edema and erythema of the posterior commissure, which is referred to as posterior laryngitis. Additional reported changes are vocal cord edema, pseudosulcus vocalis (edema of the undersurface of the vocal fold), presence of thick endolaryngeal mucous, lymphoid hyperplasia of the posterior pharynx (cobblestoning), and much more rarely granuloma formation, contact ulcers, subglottic stenosis, posterior glottic stenosis, and strictures. To provide a more consistent way of reporting fiber-optic laryngoscopy findings, Belafsky et al. created a reflux finding score (RFS) in 2001 [10]. RFS, however, has not become a useful diagnostic tool because of poor correlation between its scores and the clinical symptoms, pH probe results, and response to therapy.

Chest Imaging and Pulmonary Function Tests

In cases of chronic cough, a careful history should be obtained to rule out chronic respiratory infections and other noninfectious chronic respiratory conditions. Imaging studies, such as a chest X-ray or chest CT and pulmonary function tests, have to be performed to help make the diagnosis.

Dual pH Probe with Impedance Monitoring

Classic esophageal pH probe studies have major diagnostic and practical limitations. A large international study performed in a primary care setting showed that standard pH probe testing failed to diagnose approximately one-third of patients with established acid reflux disease. Standard esophageal monitoring for LPR is not very sensitive.

Dual pH probe and impedance monitoring can be helpful in diagnosing LPR. The proximal probe is located near the upper esophageal sphincter. A major challenge with dual pH measurement is achieving the optimal location of the upper esophageal probe in relation to the upper esophageal sphincter (UES). If the placement is too low or too high in relation to the UES, the test may show falsely positive or negative results.

An alternative to esophageal pH probes is the pharyngeal pH probe test (Restech system), which measures acid exposure in mid-pharynx. This probe is easy to place, well-tolerated, and potentially more sensitive than traditional esophageal pH testing, capable of detecting liquid and aerosolized droplets. Studies with oropharyngeal pH probes are encouraging though more data in the form of randomized controlled studies are needed [11, 12].

The benefits of the oropharyngeal pH probe are relatively low cost, ease of placement, and minimal discomfort to the patient.

Esophagogastroduodenoscopy (EGD)

Even though EGD does not prove or disprove the diagnosis of LPR, it still plays an important role in patient's assessment and formulating a management plan.

EGD can show the presence of hiatal hernia, active esophagitis, strictures, Schatzki rings, Barrett's esophagus, and other less common esophageal disorders such as achalasia or eosinophilic esophagitis. It also helps to rule out malignancy. EGD is an important preoperative assessment tool in LPR patients who are appropriate candidates for surgical anti-reflux procedures. Some studies have shown that endoscopic symptoms of severe GERD increase the probability of LPR diagnosis.

Pepsin Detection

As we have already discussed, pepsin is not native to the oropharynx or esophagus. Detection of pepsin in the oropharynx is thus indicative of reflux. A recent systematic review reported that pepsin is a reliable marker for diagnosing LPR [13]. Pepsin can be found in trace amounts in the upper aerodigestive tract in healthy asymptomatic individuals but at much lower levels when compared with LPR patients.

A few years ago, a new diagnostic tool, Peptest, emerged which has been available in the UK and Europe and has just been approved by the FDA in the USA in 2017. Peptest is an in vitro lateral flow device that uses monoclonal antibodies to detect pepsin in samples of coughed up saliva/respiratory secretions. Peptest has been shown to be highly accurate and has validated performance measures in detection of GERD. Its sensitivity and specificity are reported to reach 87% [13, 14]. It has a positive predictive value of 85% and negative predictive value of 68% in a blinded study where GERD was confirmed using pH measurement and EGD [14].

Trial of Pharmacotherapy and Reflux Precautions

Good clinical response to empirical therapy with PPIs and H2 blockers can be used to help in the diagnosis of LPR. Good response to treatment may help in avoiding excessive testing and provide quick relief to the patient. Lack of convincing response to acid suppressants and reflux precautions within 4–8 weeks of treatment should prompt the physician to investigate further and clarify the diagnosis.

In spite of many conflicting studies regarding efficacy of these treatments, there is a general consensus to conduct an initial empirical treatment with proton pump inhibitors (PPIs) twice a day for 2–3 months. Good clinical response is considered to be a diagnostic confirmation. Medications, however, reduce only the production of acid in the stomach, but non-acid or weakly acidic reflux may still persist. This may explain the fact that multiple studies show that failure of treatment even with high-dose acid suppression (PPIs given twice a day) may reach up to 30% of cases.

Treatment

Lifestyle Modification

Lifestyle and dietary modifications can be of very significant help in many cases and should be strongly recommended to all patients. Cessation of smoking, stopping alcohol and coffee use, complete avoidance of carbonated drinks, weight loss,

no eating before lying down, and elevation of the head of the bed by 4–6 inches are universal recommendations. Avoidance of reflux-triggering foods such as coffee, chocolate, vinegar, mint, fatty and spicy foods, citrus fruits, tomatoes and their products, fresh onions, and garlic can greatly reduce symptoms and significantly augment the effects of medical therapy. There are several books available for the general public that deal especially with the dietary recommendations for patients in GERD and LPR.

Medical Therapy

PPIs are the first-line treatment in pharmacological management of LPR. These medications can provide significant relief for many patients with LPR and have shown their superiority over lifestyle modification alone in alleviating symptoms in LPR patients. PPIs have been shown to improve the RSI scores in LPR patients compared to the placebo-treated group. This is supported by strong evidence both by randomized trials and meta-analyses. Response to treatment, however, has been variable [15–18].

There is still no agreement on what should be the recommended duration of the initial treatment with PPIs. Recommendations vary anywhere between 6 and 12 weeks based on improvement in symptoms and RSI scores. Many patients are unable to stop PPIs due to quick recurrence of symptoms.

Recently, there has been increasing concern regarding the adverse effects of PPIs. Reports of adverse outcomes with long-term PPIs include nephritis, osteoporosis with risk of bone fractures, dementia, increased risk of *C. difficile* infection, and premature death [19]. In light of these reports, the treatment duration of PPIs and risk benefit of long-term treatment should be carefully weighed.

H2 blockers and antacids are used as an adjunct therapy and have limited role as sole therapy in the management of LPR.

Prokinetic agents have also been studied in combination with PPIs in treatment of LPR. The data is not strong for recommendation of prokinetic agents in addition to PPIs.

Endoluminal Treatment

Various endoluminal devices have been approved by FDA for treatment of GERD. These include EsophyX® transoral incisionless fundoplication device, LINX® magnetic beads system, and Stretta® procedure.

EsophyX® is a transoral incisionless fundoplication (TIF) device. There is some data to support the effectiveness of EsophyX® in treating patients with LPR with subsequent improvement in RSI or atypical symptoms. TIF also lead to significant decrease in PPIs use in treated patients. Limited data is available on long-term durability of this treatment. Serious adverse outcome is reported anywhere between 0.14% and 4% [20, 21].

Stretta® procedure is an endoscopic therapy which delivers radiofrequency energy to the lower esophageal sphincter muscle. This causes remodeling of muscle fibers and improved LES function. There is paucity of literature regarding the Stretta® procedure for LPR. In one study, the Stretta® procedure has been shown to be equally effective in improving symptoms of LPR and decrease in use of PPIs [22].

Both abovementioned endoluminal therapies have not shown superiority when compared to 360 degree (Nissen) fundoplication. Some studies have shown inferior results when compared with Nissen fundoplication, whereas others have shown these to be equivalent to partial (Toupet and Dor) fundoplication.

More data on long-term follow-up of endoluminally treated patients is needed to decide the effectiveness of these treatment strategies.

Surgical Therapy

Fundoplication or Anti-Reflux Surgery

Anti-reflux surgery has been reserved as a treatment modality for medically refractory LPR, patients who do not want to take long-term PPI, and severe GERD associated with LPR.

Preoperative planning and workup is an essential prerequisite for anti-reflux surgery.

EGD is usually the initial step. A barium esophagogram helps in assessing the anatomical and, perhaps, functional aspect of the esophagus and helps in ruling out achalasia and large hiatal hernias. It serves as a good test for follow-up post anti-reflux surgery.

Esophageal manometry is important in determining presence of achalasia and other motility disorders of the esophagus. One should proceed to full fundoplication (Nissen) only if the motility is normal (>70% normal swallows). Otherwise, one should do a partial fundoplication (commonly Toupet).

Dual pH monitoring and impedance measurement with or without oropharyngeal pH monitoring support LPR diagnosis and are usually part of preoperative workup.

A laparoscopic Nissen fundoplication is a standard 2–3-cm-long, complete 360 degree loose gastric fundal wrap, whereas a Toupet fundoplication is a 270 degree partial wrap. Anti-reflux surgery has good outcomes in carefully selected LPR patients, but the results are slightly inferior when compared with GERD outcomes [23].

Cough has been shown to improve after anti-reflux surgery. The response rate is variable anywhere between 30% and 80% in literature. The difference between Nissen and Toupet in relieving cough symptom of LPR has been shown to be not significant in one study [24].

Hoarseness, one of the common symptoms of LPR, is also shown to improve after anti-reflux surgery. The data is limited, and no trials have been done to compare various surgical techniques.

The above statements are supported by Brown et al. in a large prospective study which reported significant improvement in atypical symptoms of GERD, cough,

wheeze, and hoarseness, in patients undergoing anti-reflux surgery (Nissen) for GERD [25].

Zhang et al. reported improvement in RSI score in LPR patients after Nissen fundoplication when compared with PPI group. LPR was diagnosed using oropharyngeal pH monitoring and using high-resolution manometry and endoscopy for associated GERD [26]. At 2-year follow-up, independence from PPI was marked in surgery group, and overall satisfaction was better in surgery group.

Complaints of shortness of breath and difficulties with breathing (often associated with asthma) have also been shown to improve with surgery (Nissen fundoplication) when compared with medical treatment group [27], with a decrease in beta-agonist, and oral corticosteroid use in asthmatics has also been reported after Nissen fundoplication [28].

New Frontiers

Epidermal growth factor (EGF) is a cell growth-stimulating cytokine and plays a role in cell differentiation. It can be a potential marker for LPR diagnosis. Salivary EGF levels were found to be low in patients with reflux laryngitis (LPR) when compared with healthy controls. But there was no change in EGF level posttreatment [29].

The following biomarkers have been identified in medial arytenoid biopsy specimens of LPR patients: (1) mucosal defense markers MUC2, MUC5B, and CDH1, (2) squamous/columnar marker KRT14, and (3) inflammatory markers CD1d, CRNN, and TGFb-1. These biomarkers have promising potential in identification and probably in the diagnosis of LPR [30].

Conclusion

Despite having a significant disease burden, the awareness of LPR in the medical community remains low. As a result, it is underdiagnosed and undertreated. LPR requires a high degree of clinical suspicion and experience on behalf of the physician to diagnose and treat. For patients who do not respond to medical therapy, laparoscopic fundoplication offers great relief of symptoms.

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